
Cellular epigenetic diversity as a blueprint for defining the identity and functional potential of human embryonic stem cells

Grant Award Details

Cellular epigenetic diversity as a blueprint for defining the identity and functional potential of human embryonic stem cells

Grant Type: SEED Grant

Grant Number: RS1-00245

Investigator:

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Institution:	University of California, Los Angeles
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: \$549,698

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Cellular epigenetic diversity as a blueprint for defining the identity and functional potential of human embryonic stem cells

Public Abstract:

Human embryonic stem (ES) cells have the capacity to self-renew but also give rise to other cell types. How this capacity is regulated and what factors determine one fate over another is an active area of research. This is because by understanding the decision making process the a stem cell goes through, we might be able to manipulate the process and make stem cells generate more of themselves or other cell types of interest. Preliminary studies indicate that one important determinant of stem cell fate is its 'epigenetic' information content.

In humans, DNA is tightly wrapped around a core of proteins called histones to form chromatin—the physiologically relevant form of the genome. The histones can be modified by small chemical molecules which can affect the structure of chromatin, allowing for a level of control on gene expression. The patterns of occurrences of the histone modifications throughout chromatin is highly regulated and can increase the capacity of the genome to store and process biological information beyond the DNA sequence. This information which is heritable but not encoded in the sequence of DNA is referred to as 'epigenetics.' The modifications of histones, therefore, contribute to the epigenetic information content of a human ES cell.

We have found that individual ES cells from mouse have different patterns of histone modifications, and thus, different epigenetic information content. We believe these differences may affect the fate decisions of stem cells. If so, then the histone modifications may act as a natural indicator of the potential of ES cells to make certain fate decisions. The histone modifications may also provide a natural tool by which cell fate decisions can be influenced. In this proposal, we intend to determine the epigenetic information of content of several human ES cell lines and relate that information to the potential of cells to make self-renewal versus differentiation decisions. Our work will provide a fast and high-throughput measure by which appropriate ES cells can be chosen for a clinical application of interest.

Statement of Benefit to California:

The available human embryonic stem (ES) cell lines display different capacities to proliferate to either generate more of themselves or differentiate to other cell types. Epigenetic regulatory mechanisms play critical roles in these developmental decisions, such as how a given cell establishes and maintains its identity. The identity of a pluripotent stem cell, such as an ES cell, is defined as being able to differentiate to all tissues of the body, yet, being able to switch off this differentiation process, otherwise, its self-renewal ability, or "stemness", is lost. There have also been observations that certain ES cell lines are better at resisting spontaneous differentiation, or more efficient in making particular cell types such as those of blood, than other lines. It is conceivable that this kind of variability in ES cell lines is likely linked to underlying epigenetic differences. Currently, there is no rapid or reliable way to scan epigenetic differences between different ES cell populations, as current methods are either too laborious to perform on daily basis, or contain very little biological information. Our work proposes to develop a natural, fast and high-throughput tool for measuring cellular epigenetic patterns, which we hypothesize to be linked not only to the identity of various differentiated cell types, as we have shown already, but also to define the quality or functional potential of various ES cell lines. It is important to understand and be able to measure the capacity of various ES cells so that appropriate cells are chosen for a clinical application of interest. This would be beneficial to the people of California because ES cells can be quality controlled before they are used in patients.

Furthermore, if epigenetic modifications that link to cellular identity and functional potential become useful diagnostic tools, the approaches discussed in this project may lead to innovative discoveries and patents that may be exploited by the biotech industry in California, and thereby improve the economy of California.